Season of birth and risk of brain tumors in adults

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Abstract—*Background:* Recent studies demonstrated an excess of winter births in children with brain tumors and in adults with various neurologic or psychiatric diseases relative to the general population. *Objective:* To investigate a possible association between month of birth and risk of brain tumors in adults using data from a large, hospital-based case-control study. *Methods:* Cases were patients with incident glioma (n = 489) or meningioma (n = 197) diagnosed at hospitals in Boston, MA, Phoenix, AZ, and Pittsburgh, PA. Controls (n = 799) were patients hospitalized for a variety of nonmalignant conditions and frequency matched to cases by hospital, age, sex, race/ethnicity, and distance of residence from hospital. Odds ratios (ORs) were calculated using multivariate unconditional logistic regression allowing for cyclic variation in risk with month of birth. *Results:* A relationship between month of birth and risk of adult glioma and meningioma was found, best described by a 12-month periodic function with peaks in February and January and troughs in August and July. The association between month of birth and risk of glioma differed significantly by handedness, with left-handed and ambidextrous subjects born during late fall through early spring being at particularly high risk of adult glioma as compared with those born at other times of the year. *Conclusion:* These findings suggest the importance of seasonally varying exposures during the pre- or postnatal period in the development of brain tumors in adults.

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Recent epidemiologic studies conducted in the United Kingdom and Norway suggested an association between childhood brain tumors, primarily astrocytic tumors, and season of birth.[1,2] An excess of winter births and deficit of summer births were observed among children with brain tumors as compared with the general population. Many neurologic and psychiatric diseases in adults are reported to have specific seasonal birth patterns as well.[3] For example, epilepsy consistently has been shown to have an excess of births from December through March and a deficit of births in September.[4,5] Schizophrenia,[6-9] bipolar disorder,[9,10] Alzheimer disease,[3,11] and narcolepsy[12] have also demonstrated excesses of winter births, whereas multiple sclerosis appears to be associated with birth during April, May, or June.[13] In addition, there have been reports of seasonal variation in risk of other cancers, including acute lymphoblastic leukemia in children,[14,15] early-onset Hodgkin lymphoma,[16] breast cancer,[17,18] and testicular cancer.[19] The high sensitivity of the CNS to environmental exposures in utero and during infancy[20,21] and the long latency from initiation to clinical onset for many neurologic diseases[3] raise the possibility that seasonally varying exposures acting very early in life might influence the risk of brain tumors in adulthood. In the current analysis, we tested the hypothesis that the risk of adult glioma and meningioma is associated with month of birth, using data from a large, hospital-based case-control study of brain tumors conducted at three US hospitals. We also addressed whether an effect of season of birth on risk of brain tumors is influenced by other factors that might be related to events early in life.

Materials and methods. *Study population and setting.* Methods were described in detail previously.[22] In brief, the study was conducted between June 1994 and August 1998 at Brigham and Women's Hospital in Boston, MA, St. Joseph's Hospital and Medical Center in Phoenix, AZ, and Western Pennsylvania Hospital in Pittsburgh, PA. Eligible cases were patients newly diagnosed with histologically confirmed intracranial glioma or neuroepithelomatous tumors (n = 489; International Classification of Diseases [ICD]-O-2 codes 9380 to 9473 and 9490 to 9506) or meningioma (n = 197; ICD-O-2 9530 to 9538) at the participating hospitals. Cases had to be at least 18 years old and reside within 50 miles of the hospital (or within Arizona for the Phoenix hospital) at the time of diagnosis and understand English or Spanish. Of the potentially eligible cases invited to participate in the study, 88% of glioma cases and 94% of meningioma cases agreed to do so. Among patients with glioma, there were 135 low-grade and 354 high-grade tumors.[23] Sixty-three percent of the low-grade gliomas were oligodendroglioma, astrocytoma, or mixed glioma, and 86% of the high-grade gliomas were glioblastoma or anaplastic astrocytoma. Among patients with meningioma, there were 2 malignant tumors and 13 atypical tumors; the remaining were benign or unspecified tumors.

Controls were patients admitted to the same hospitals as the cases for a variety of nonmalignant conditions. They were frequency matched (1:1) to a total case series by hospital, age (in 10-year strata), sex, race or ethnicity, and distance of residence from hospital. Of the potentially eligible control subjects con-

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tacted, 86% (n = 799) participated. The most common reasons for hospital admission among control subjects were injuries and poisoning (n = 197; ICD-9 800 to 999, V01 to V82, E800 to E999) and diseases of the circulatory (n = 179; ICD-9 390 to 459), musculoskeletal (n = 172; ICD-9 710 to 739), digestive (n = 92; ICD-9 520 to 579), and nervous (n = 58; ICD-9 320 to 389) systems.

Data collection. After informed consent was obtained, information was collected about a variety of postulated risk factors and potential confounders, including sociodemographic characteristics, by means of a computer-assisted, personal interview conducted in the hospital. Subjects were asked their date of birth at the beginning of the interview. In addition, date of birth was available from the medical record. Very few discrepancies (7 in glioma cases and 10 in control subjects) between the two sources of data were found, and these did not affect our analysis. For the current analysis, we also used data from the interview concerning the respondent's answers to questions about physician-diagnosed allergy (yes/no) or autoimmune disease (yes/no) and handedness. Handedness was defined based on the answer of each participant to the question, "Are you left-handed or right-handed?" If a respondent hesitated or said "It depends," the interviewer asked, "What hand do you write with?" Thus, subjects were classified as either right-handed or non-right-handed, with the latter category including left-handed and ambidextrous persons. Detailed analyses of associations between allergies, autoimmune diseases, and handedness and risk of brain tumors were reported previously.[24,25] Place of birth was defined as a two-level categorical variable based on average annual temperature at the state of birth (≤55/>55 °F).[26] If the state was divided between the two categories, then the temperature for the predominant part of the state was used to characterize the state as a whole. A relatively small proportion of proxy interviews was necessary when the subject was critically ill or had died: 16% for the glioma cases, 8% for the meningioma cases, and 3% for the control subjects.

Statistical analysis. The odds ratio (OR) was used as the measure of association between month or season of birth and risk of brain tumors. Unconditional multivariate logistic regression models were fitted to estimate ORs and compute 95% CIs using SAS PROC LOGISTIC (Cary, NC).[27] We evaluated the seasonality pattern first by plotting ORs and 95% CIs for each month of birth relative to October, and we tested the null hypothesis of no seasonal variation in risk of brain tumors based on a 2-*df* likelihood ratio test comparing models without and with a periodic function. The latter included simultaneous sine and cosine transformation of month of birth to allow cycles to begin at any point within the year.[28] In the preliminary analysis, we tested cycles of 12, 6, 4, 3, and 2 months, and 12 months gave the best fit. Therefore, we report all the results for a 12-month periodic function throughout the article. We also evaluated whether the estimates of the periodic function were affected by the adjustment for, or varied according to the level of, education, marital status, place of birth, handedness, birth order, and history of allergy or autoimmune disease. As the adjustment did not materially change our results, we present final data based on the models including only the matching variables. If there was a suggestion that seasonality effect differed by the levels of the tested factors, we present estimates for January to March, April to June, July to September, and October to December separately for each level of the factor of interest. All subjects born in the Southern Hemisphere or having unknown place of birth (five glioma cases, three meningioma cases, and five control subjects) were excluded to ensure qualitatively similar seasonal patterns. Test of no differences in seasonality pattern between low-grade and high-grade glioma as described by periodic function was based on a 2-*df* likelihood ratio test comparing models without and with sine and cosine transformation of month of birth among glioma cases only. The sensitivity of the results to types of conditions or illnesses included in the control series was evaluated by successively excluding subgroups with different reasons for hospital admission (trauma, diseases of circulatory, musculoskeletal, digestive system, or all others combined) and refitting the regression models.

Results. Detailed descriptions of study subjects were presented elsewhere.[22,29] In brief, the average age at diagnosis was 52 years for glioma patients and 55 years for meningioma patients, and the average age at hospital admission was 50 years for control subjects. The male/female ratio among cases was 1.3 for glioma, 0.3 for meningioma, and 0.8 among control subjects. Glioma, but not meningioma, cases were more likely to have graduated from college or professional school than control subjects. Both glioma and meningioma cases tended to be married at the time of tumor diagnosis (or enrollment in the study) more often than control subjects.

The observed and fitted ORs for glioma in relation to month of birth are plotted in figure 1. A formal test of periodicity was consistent with seasonal variation in glioma risk ($\chi^2 = 6.096$ with 2 *df*, $p = 0.04$). We estimated that the natural logarithm of the month-specific odds was best described by a cosine function with amplitude of 0.21, peak in February and trough in August, resulting in a peak-to-trough OR of 1.5. Similar to glioma, risk of meningioma exhibited cyclic variation according to month of birth ($\chi^2 = 6.182$ with 2 *df*, $p = 0.04$). The estimated amplitude of the periodic function was 0.30 with peak in January and trough in July and a peak-to-trough OR of 1.8. The observed and fitted ORs for meningioma are presented in figure 2. Excluding different diagnostic subgroups of controls from the analysis did not materially change the estimated parameters of the periodic function for glioma or meningioma (data not shown).

Separate analysis by grade of glioma suggested that a periodic function, similar to that obtained using all glioma cases, improved the model fit significantly for high-grade glioma but not for low-grade glioma: OR = 1.12*exp(0.25*cos[(month*2π/12) − 1.0]). However, differences in seasonality pattern by tumor grade were not significant.

Based on summary statistics for the joint effects of month of birth and selected characteristics (table 1), we present risk estimates for glioma with season of birth by handedness (table 2) and history of autoimmune disease (table 3) and for meningioma by sex (table 4). Births from October through March were associated with especially high risk of glioma among left-handed and ambidextrous subjects (see table 2) as compared with births from July through September. Interestingly, the proportion of non-right-handed individuals was lower ($p < 0.001$) among control subjects born in fall or winter (10%) than among control subjects born in spring or summer (20%, data not shown). For subjects with a history of autoimmune disease, there was a suggestion that risk of glioma had an opposite seasonal pattern compared with subjects without history of autoimmune disease (see table 3). Finally, males born from October through December were at higher risk of meningioma than males born at other times of the year (see table 4).

Discussion. A significant relationship between month of birth and risk of adult glioma and meningioma, best described by a 12-month periodic function with peaks in February and January and troughs in August and July, was found in this large, hospital-based case-control study. The association between month of birth and risk of glioma significantly differed by handedness, with left-handed and ambidextrous subjects born during late fall through early spring being at particularly high risk of adult glioma as compared with those born at other times of the

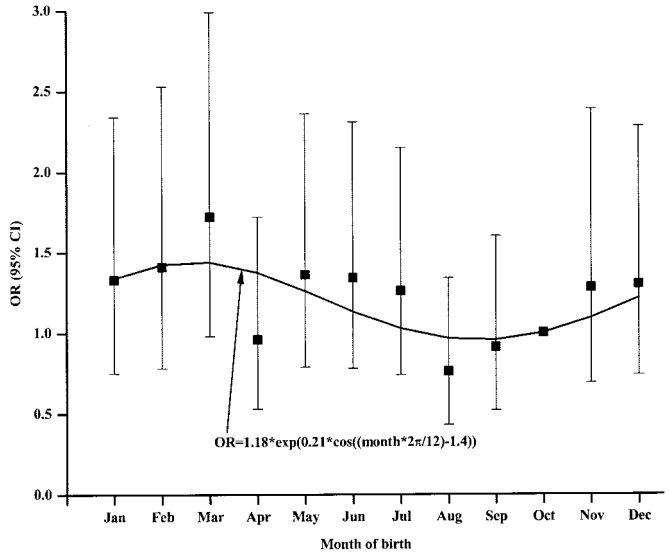

Figure 1. Observed and fitted odds ratios (ORs), with 95% CIs, for risk of adult glioma by month of birth: hospital-based case-control study conducted in Boston, Phoenix, and Pittsburgh, 1994 to 1998. October is referent month.

year. Also, there was a suggestion that the effect of season of birth on risk of glioma differed by history of autoimmune disease and that the effect of season of birth on risk of meningioma differed by sex.

The central focus of the analysis was on month of birth, which was obtained from medical records as well as interview. It is unlikely that results were influenced seriously by errors in recall or reporting of month of birth related to cognitive impairment of some cases or inclusion of proxy responders. Statistical methods for studying seasonal patterns were applied with adjustment for a variety of potential confounders.[28] Yet, the possibility of uncontrolled confounding remains, as we lacked data on other perinatal factors that might influence risk of adult brain tumors, and little is known about what exposures later in life might be associated with month of birth. An important concern of the study was the potential for selection bias if there was an association between month of birth and probability of becoming a hospital control. However, our controls were chosen from patients hospitalized for a variety of nonmalignant conditions, and the major diagnostic subgroups of controls were not appreciably different with respect to month of birth. Furthermore, excluding any of them from the analysis had little influence on the periodicity tests and estimated parameters of cyclic functions. Although several of the associations with risk of glioma and meningioma were significant, they were of modest strength and we cannot exclude the possibility they were due to chance.

There have been earlier reports of a relationship between season of birth and risk of childhood brain tumors.[1,2] A study conducted in the United Kingdom[1] found an excess of cases born in late fall or winter for astrocytoma and ependymoma, and a study conducted in Norway[2] found an excess of cases born in winter for all brain tumors. Interestingly, in the Norwegian study,[2] the rate ratio (RR) for children born in winter relative to those born in spring increased with attained age and was highest in the 11- to 15-year-old group (RR = 2.68). The distribution of major brain tumor types changes appreciably with age. Our study of adult glioma (64% of which were glioblastoma or anaplastic astrocytoma) and meningioma,

Table 1 *Summary statistics for joint effects of selected characteristics and month of birth on risk of adult glioma and meningioma: hospital-based case-control study conducted in Boston, Phoenix, and Pittsburgh, 1994–1998*

		Glioma		Meningioma	
Characteristic	*df*	χ^2	*p**	χ^2	*p*
Sex	2	1.562	0.46	5.511	0.06
Age†	4	5.899	0.21	4.782	0.31
Study center	4	2.773	0.60	3.013	0.56
Education‡	4	6.831	0.14	3.666	0.45
Marital status§	2	0.164	0.92	1.679	0.43
Place of birth‖	2	1.348	0.51	0.08	0.96
Handedness	2	6.500	0.04	1.645	0.44
Birth order¶	2	2.195	0.33	1.981	0.37
History of allergies	2	0.708	0.70	2.827	0.24
History of autoimmune diseases	2	5.618	0.06	0.037	0.98

* *p* value of interaction test.
† Based on three categories: 18–39, 40–59, and 60+ y.
‡ Based on three categories: less than high school, finished high school or 3-y college or vocational school, and 4-y college or graduate degree or professional school.
§ Based on two categories: married or living together and single (at the time of tumor diagnosis).
‖ Based on two categories: average annual temperature ≤55° F and average annual temperature >55° F.
¶ Based on two categories: first-born and other; adjusted for number of siblings.

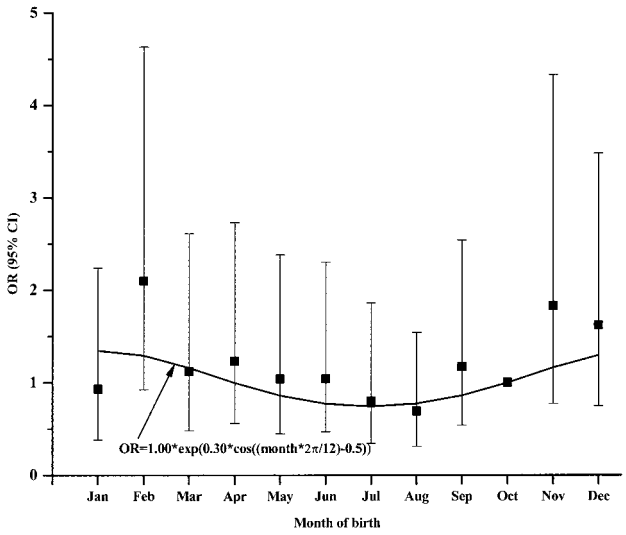

Figure 2. Observed and fitted odds ratios (ORs), with 95% CIs, for risk of adult meningioma by month of birth: hospital-based case-control study conducted in Boston, Phoenix, and Pittsburgh, 1994 to 1998. October is referent month.

which is very rare in children, also found an excess of winter births for both tumor types. Separate analysis by grade of glioma revealed significant evidence of periodicity for high-grade glioma (n = 354) but not for low-grade glioma (n = 135). However, these differences by tumor grade were not significant.

Apart from the effect of season of birth on risk of brain tumors, we were interested in whether this effect differed by categories of other factors, particularly those thought to be related to events early in life, such as place of birth, handedness, birth order, and history of allergy or autoimmune disease. We expected that a seasonality effect would vary with latitude or climate, yet there was little evidence that the seasonal pattern was modified by place of birth. However, place of birth was defined broadly as a two-level categorical variable based on average annual temperature for the state of birth.[26] In the previous analyses, we found that history of allergy or autoimmune disease, as well as left-handedness, was associated with reduced risk of glioma.[24,25] Handedness is believed to be determined very early in life,[30-32] perhaps in utero, and to vary by season of birth.[33] Indeed, we found that the prevalence of left- or mixed-handedness was substantially higher among control subjects born in spring or summer than those born in fall or winter. The analysis of joint effects revealed that left-handed or ambidextrous subjects born during late fall through the beginning of spring were at higher risk of adult glioma relative to those born at other times of the year. We also considered birth order and history of allergy or autoimmune disease, as first-borns and subjects with the above-mentioned immune abnormalities are believed to be less exposed to infections during infancy,[34] according to the "hygiene hypothesis."[34-37] There was a suggestion of an opposite seasonal pattern in risk of glioma among persons with and without a history of autoimmune disease, but no apparent difference by other factors. Evidence of interaction between month of birth and handedness, as well as history of autoimmune disease, was specific to glioma. On the other hand, males born during late fall or early winter tended to be at substantial risk of meningioma relative to males born at other times of the year.

The interpretation of these findings is not straightforward. Epidemiologic data concerning seasonality of birth and risk of brain tumors in adults or of factors that could modify these relationships are sparse. However, seasonal variation in risk of adult glioma and meningioma seems to be plausible, given current knowledge on the epidemiology of childhood brain tumors[1,2] and neurologic and psychiatric diseases in adults,[3-13] long latency from initiation to onset for many of them[3] (similar to neoplasia), and sensitivity of the CNS to environmental insults,[21] particularly at early stages of its development.[20] If confirmed in further studies, our findings might suggest the importance of events early in life in the development of brain tumors in adults and add to the theory of "fetal origin of adult disease."[38] However, it is not possible at this point to deduce what factors are responsible for the observed associations

Table 2 *Association between season of birth and risk of adult glioma by handedness: hospital-based case-control study conducted in Boston, Phoenix, and Pittsburgh, 1994–1998*

Month of birth	Handedness							
	Right				Nonright*			
	Cases, n	Controls, n	OR†	95% CI‡	Cases, n	Controls, n	OR	95% CI
Jan–Mar	108	139	1.40	0.99–1.99	17	26	3.58	1.36–10.08
Apr–Jun	115	163	1.24	0.88–1.75	16	40	2.03	0.78–5.53
Jul–Sep	110	200	1.00	Referent	10	41	1.00	Referent
Oct–Dec	95	165	1.06	0.74–1.50	13	20	3.18	1.13–9.36

* Includes left-handed and ambidextrous.
† OR = odds ratios adjusted for matching factors.
‡ 95% profile likelihood CIs.

Table 3 *Association between season of birth and risk of adult glioma by history of autoimmune disease: hospital-based case-control study conducted in Boston, Phoenix, and Pittsburgh, 1994–1998*

Month of birth	History of autoimmune disease							
	No				Yes			
	Cases, n	Controls, n	OR*	95% CI†	Cases, n	Controls, n	OR	95% CI
Jan–Mar	105	133	1.58	1.10–2.29	11	28	0.88	0.34–2.16
Apr–Jun	112	148	1.49	1.04–2.14	14	49	0.62	0.26–1.44
Jul–Sep	92	187	1.00	Referent	22	48	1.00	Referent
Oct–Dec	94	143	1.36	0.94–1.97	10	36	0.60	0.23–1.48

* OR = odds ratios adjusted for matching factors.
† 95% profile likelihood CIs.

Table 4 *Association between season of birth and risk of adult meningioma by sex: hospital-based case-control study conducted in Boston, Phoenix, and Pittsburgh, 1994–1998*

Month of birth	Sex							
	Males				Females			
	Cases, n	Controls, n	OR*	95% CI†	Cases, n	Controls, n	OR	95% CI
Jan–Mar	10	80	1.72	0.59–5.24	33	85	1.40	0.80–2.45
Apr–Jun	10	97	1.22	0.41–3.74	39	106	1.26	0.74–2.13
Jul–Sep	7	113	1.00	Referent	41	128	1.00	Referent
Oct–Dec	18	71	4.40	1.72–12.59	36	114	1.16	0.67–1.98

* OR = odds ratios adjusted for matching factors.
† 95% profile likelihood CIs.

(if real) and during what time window they might have been operating. At most, we can hypothesize that the relevant exposures should vary seasonally, though not necessarily in the same phase as risk of the disease, and they could act anywhere from the time of conception to the months following birth. The list of candidate exposures includes not only infections, many of which vary seasonally, but also maternal diet, environmental toxins, photoperiod, temperature, weather, and hormonal milieu.

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